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Medical therapy for preventing recurrent endometriosis after conservative surgery: a cost-effectiveness analysis

Running title: Economic analysis of preventing endometriosis

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Abstract

Objective: To assess the cost-effectiveness of different strategies, including the gonadotropin-releasing hormone agonist (GnRH-a) and oral contraceptive therapy, for the prevention of endometriosis recurrence after conservative surgery.

Design: Cost-effectiveness analysis from a health care perspective.

Setting: Chinese setting represented as a health resource limited setting.

Population: patients who undergo laparoscopic or laparotomic conservative surgery for endometriosis.

Methods: A Markov model was developed for the disease course of endometriosis. Clinical data were obtained from published studies. Direct medical costs and resource utilization in the Chinese health care setting were taken into account. The health and economic outcomes were evaluated over a period from treatment initiation to menopause onset. Sensitivity analyses were carried out to test the impact of varied parameters and assumptions on the model output.

Main outcome measures: Quality-adjusted life years (QALYs) gained and costs from a health care perspective.

Results: The incremental cost effectiveness ratio of 6-month GnRH-a therapy compared with no therapy ranged from $6,185 per QALY in deep endometriosis to $6,425 with in peritoneal endometriosis The incremental cost effectiveness ratio of 6-month GnRH-a therapy compared with no therapy ranged from $6,185 per QALY in deep endometriosis to $6,425 with peritoneal endometriosis. A one-way sensitivity analysis showed considerably influential factors, such as remission rates and utility values. Probabilistic sensitivity analysis indicated that 6-month GnRH-a therapy is cost-effective in most cases at a threshold of $7,400/QALY, regardless of the type of endometriosis.

Conclusion: Six months of therapy with GnRH-a can be a highly cost-effective option for the prevention of endometriosis recurrence.

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Keywords: endometriosis; gonadotropin-releasing hormone agonist; recurrence; cost-effectiveness

Tweetable abstract: Gonadotropin-releasing hormone agonist for the prevention of endometriosis recurrence is cost effective.

Introduction

Endometriosis is defined as the presence of endometrial tissue at sites other than the uterine cavity, such as the ovaries, fallopian tubes, pelvis, and abdomen [1, 2]. It affects up to 10% of the general population[3, 4]. Recent studies also showed that women with endometriosis may have an increased risk of epithelial ovarian cancer[5]. Due to chronic symptoms (dyspareunia, dysmenorrhea, chronic pelvic pain, and dyschezia) and infertility, endometriosis can significantly affect not only the health-related quality of life but also the consumption of resources available in the health systems and indirect costs[6]. The aims of medical therapy are to mitigate symptoms, inhibit progression, and reduce the recurrence of symptoms and disease after surgery, which involves removing visible areas of endometriosis and restoring the anatomy[7]. Due to its proven efficacy in reducing pain, the recommendation to clinicians is to surgically manage endometriosis when endometriosis is identified at laparoscopy[7]. However, recurrence after surgery remains a challenge, as up to 50% of patients will experience recurrence by the 5‐year follow-up because surgery does not affect the pathogenic mechanisms of endometriosis[8]. Various options, such as oral contraceptives, have been tested after surgery to maintain the clinical effects of surgery on symptoms[2, 8, 9]. Gonadotropin-releasing hormone agonist (GnRH-a), considered the most 'powerful' compound, was superior to expectant or placebo treatment in the prevention of recurrence[10]. Compared with oral contraceptive therapy, GnRH-a therapy has better clinical benefits but is more expensive. The decision to use GnRH-a therapy should be made according to cost, availability, and the patient's preference with respect to the delivery method[11].

There is only one published economic analysis from UK which compared different treatments for preventing the recurrence of endometriosis, including the levonorgestrel-releasing intrauterine system, depot-medroxyprogesterone acetate, combined oral contraceptive pill, and no medical therapy[12]. However, no studies that we were aware of investigating the cost-effectiveness of GnRH-a therapy. Although GnRH-a is often administered as a second-line option, it has received much attention and is prescribed frequently as a first-line option after the surgery in recent years due to its improved effectiveness and reduced recurrent episodes[1, 13]. Therefore, the objective of this study was to evaluate the cost-effectiveness of GnRH-a and oral contraceptive therapy versus usual care for ovarian, peritoneal, deep, and other endometriosis after conservative surgery. The perspective of the Chinese health care system, representative of a health resource-limited setting, was adopted in this analysis, and only direct medical costs were considered.

Materials & methods

Analytical overview and model structure

A mathematical model was developed to evaluate the cost-effectiveness of different strategies for the prevention of recurrent endometriosis in women who undergo laparoscopic or laparotomic conservative surgery for endometriosis. Patients were grouped according to one of the four competing strategies to prevent recurrent endometriosis (Figure 1A): 1) no medical therapy (Control strategy); 2) oral contraceptive therapy (OC strategy); 3) three months of GnRH-a therapy (GnRH-3 strategy); and 4) six months of GnRH-a therapy (GnRH-6 strategy). After GnRH-a therapy was finished, we assumed that an oral contraceptive would be administered[7]. Once the endometriosis relapsed, patients were retreated with surgery and/or hormonal therapy[1]. Health and economic outcomes were projected using the Markov process (Figure 1B), with five exclusive health states: normal life, disease recurrence with medical therapy, disease recurrence with surgery, ovarian cancer, and death. Because endometriosis is best managed with long-term medical suppression and long-term postoperative suppression is a barrier to conception[14], the pregnant outcome is not considered in the model for focusing the study aim and simplifying the model. Because the GnRH-a was administered once per month for preventing the recurrence of endometriosis, the Markov cycle length was set to be one month. The initial health state for all women after surgery was normal life. During each Markov cycle, patients may transit to a new health state (straight arrow). This economic analysis was based on a literature review and modelling techniques; it did not require approval by the Institutional Research Ethics Board.

The base-case initial age of the hypothetical cohort with diagnosed endometriosis and subsequently underwent conservative surgery were 32 years, which were assumed to be similar with the epidemiological study of the Chinese women with endometriosis[15]. Because endometriosis patients usually enter regression during menopause, the current analysis assumed that menopause onset was the end of the model[16]. The base-case age of menopause in Chinese women is 50 years [17]. The impact of the base-case initial and menopause age would be tested in the sensitivity analyses by using the range of 21–50 and 41-62 years, respectively.

The primary outcome measures were quality-adjusted life-years (QALYs) and cost, which were annually discounted at 5%, in line with the Chinese guidelines for pharmacoeconomic evaluations[18]. Incremental cost-effectiveness ratios (ICERs), presented as cost per additional QALY gained, were calculated. When the ICER was lower than the per capita gross domestic product (GDP) of China per QALY gained ($7,400/QALY), the intervention was considered to be cost-effective[19].

Clinical data

The recurrence rates of deep, ovarian, and pelvic endometriosis after surgery were obtained from a long-term cohort study, which included consecutive women with a first diagnosis of endometriosis who underwent laparoscopic or laparotomic conservative surgery for endometriosis[20]. The recurrence rates of deep, ovarian, and pelvic endometriosis was showed in the scenario of no medical treatment after surgery for the $\leqslant$4 years and 5-8 years, respectively. To extrapolate the effects beyond the time period of the cohort study, we assumed that the recurrent probabilities from year 9 until the end of the model was same with the estimated data for year 8. The relative risks (RRs) of the recurrence rates of oral contraceptive therapy versus no medical prevention and treatment with GnRH-a for 3 and 6 months versus oral contraceptive therapy were estimated based on the results of two meta-analyses [10, 21], which reported odds ratios (ORs) that were converted to RRs using a well-accepted method[22]. Because the duration of

efficacy of GnRH-a treatment was assumed to be no more than 1 year[23], the current analysis used 6 and 12 months as the durations for the GnRH-3 and GnRH-6 strategies based on expert opinion. Once the disease recurred, nearly 51% of patients received a second surgery and the rest of the patients received medical therapy[24]. For those receiving a second surgery, the analysis assumed, according to expert opinion, that the 6-month GnRH-a treatment would be prescribed to prevent further recurrence. Due to the increased risk of ovarian cancer in patients with endometriosis, the current analysis also considered the impact of this consequence[25]. The annual incidence of ovarian cancer in China is 5.35/100,000[26], which was adjusted based on the reported OR (1.46, 95% CI: 1.31–1.63) for women with endometriosis[25]. The five-year survival rate in Chinese women with ovarian cancer was 65.3% (95% CI: 61.8-68.8%)[27]. A nested case-control study based on the data from the National Swedish Cancer Register showed the OR of radical extirpation of all visible endometriosis and ovarian cancer to be 0.30 (95% CI: 0.12-0.74), and simple medical therapy without surgery did not provide benefits with respect to reducing the risk[28]. Thus, we assumed the risk of ovarian cancer in women with recurrent disease was same with the patient not receiving surgery, and women without recurrence would keep the low risk throughout surgery (Table 1).

Natural mortality could be incurred by patients with endometriosis at any point in the disease course. The model used a normal life table of China from the life tables for WHO member states (2011).

Cost and utility

This analysis was conducted from the perspective of the Chinese health care system. Costs are presented in 2015 US dollars (US $ 1 = Chinese Yuan 6.5). Direct medical costs were incorporated into the model, including costs related to endometriosis treatment and follow-up, direct medical costs related to endometriosis comorbidities, and direct non-medical-related costs. All of the health resource unit costs were estimated from the literature and based on the local setting (Table S1).

The costs of GnRH-a and oral contraceptive therapy were extracted from the published literature, which incorporated cost data from nearly 130 Chinese patients with endometriosis and included the monthly overall cost of therapeutic drugs, physician consultations, and diagnostic procedures [29]. The price of triptorelin was used to estimate the cost of the GnRH-a strategy because it was widely used in Chinese clinical practice for treating endometriosis[30]. Tibolone (1.25mg daily) was used as the add-back therapy with GnRH analogues. Because of the lack of consensus on the duration of oral contraceptive therapy, it was assumed that patients would continue this therapy until menopause to prevent ovarian cancer[31]. The cost of surgical management for endometriosis was derived from published Chinese reports, which retrospectively analyzed the costs of 1,446, 4,836, 305, and 255 cases of peritoneal, ovarian, deep, and other endometriosis, respectively[32]. The annual cost of managing ovarian cancer was derived from a published study, which used the medical record data based on random cluster sampling [33].

Due to the absence of reported Chinese-specific utility values for endometriosis and ovarian cancer, the utility values of the three endometriosis states were derived from the study by Sanghera S and colleagues using a 0–10 scale as a pragmatic method and collecting the data from clinicians[12]. Due to the similar understanding and experience of this disease among clinicians in the world, these utility scores could be assumed to represent local patients, and their uncertainties were examined in sensitivity analyses (Table S1). The ovarian cancer utility values were obtained from the study by Manchanda R. and colleagues[34].

Sensitivity analyses

Sensitivity analyses are typically performed to test whether a model has any structural errors (i.e., to ensure that it is robust) and to evaluate how outcomes are affected when specific variables are adjusted. One-way sensitivity analyses were carried out to test the impact of input variables in the model on the robustness of the outputs over the ranges (Tables 1 and S1) obtained from the published literature or assuming ±25% of base case values when reported data were not available. A probabilistic sensitivity analysis (second-order Monte Carlo simulation) was performed using 1,000 simulations to simultaneously measure the impact of uncertainty caused by all variables. Probabilities, proportions, and utilities were assumed to follow a beta distribution, whereas cost was sampled from a triangle distribution owing to the limited number of samples for generating the cost data. The results are presented on a cost-effectiveness plane. The results projected from all 1,000 simulations were used to plot willingness-to-pay (WTP) acceptability curves.

Results

Base-case analysis

In the base-case analysis (Table 2), recurrence prevention with GnRH-6 compared with the other three alternatives yielded the best clinical outcomes at a higher cost for all four types of endometriosis. The cumulative probabilities of ovarian cancer were reduced by approximately 0.1% in the GnRH-6 strategy compared with the other strategies. The incremental costs of the OC, GnRH-3, and GnRH-6 strategies versus the control strategy ranged from $5,257 to 6,872, $5,467 to 7,069, $4,853 to 6,452, and $5,341 to 6,954 in patients with ovarian, peritoneal, deep, and other endometriosis, respectively, and the projected incremental gains in QALYs varied from 0.49 to 1.08, 0.51 to 1.10, 0.46 to 1.04, and 0.50 to 1.09, respectively. The ICERs of the OC, GnRH-3, and GnRH-6 strategies over the control strategy were $10,684, 7,709 and 6,364 , respectively, for ovarian endometriosis; $10,630, 7,759 and 6,425, respectively, for peritoneal endometriosis; $10,589, 7,523 and 6,185 , respectively, for deep endometriosis; and $10,728, 7,759 and 6,407 , respectively, for other endometriosis. GnRH-6 strategy was showed as a dominant strategy, and OC and GnRH-3 strategies were extended dominated (i.e., lower costs and higher ICERs) by GnRH-6 strategy (Figure S1).

Sensitivity analysis

In the one-way sensitivity analysis, the tornado graph (Figure S2) presents the results of the GnRH-6 strategy versus the control strategy for ovarian endometriosis because this type of endometriosis is the most common type and the type for which the GnRH-6 strategy could yield the greatest health benefits. The sensitivity analysis revealed that the results were sensitive to the parameters associated with the remission rate and utilities. Other parameters, such as the cost of GnRH-a and oral contraceptive therapy, had no substantial impact on the results.

Pursuant to a probabilistic sensitivity analysis, acceptability curves show that recurrence prevention with the GnRH-3 strategy, compared with no medical therapy, the OC strategy, and the GnRH-6 strategy, yielded acceptable ICERs in most cases at the threshold of the Chinese per capita GDP ($7,400/QALY) for all four types of endometriosis (Figures 2). When 3 times the Chinese per capita GDP ($22,200/QALY) was used as the threshold, the GnRH-6 strategy became more cost-effective.

Discussion

Main findings

The results of the analysis indicated that the costs per QALY gained with the GnRH-a 6-month therapy over no medical therapy varied from $6,185 for deep endometriosis to $6,425 for peritoneal endometriosis, which are both below the per capita GDP of China ($7,400 in 2015) and are thus highly cost-effective according to World Health Organization (WHO) recommendations. Of the two GnRH-a strategies, the 6-month GnRH-a therapy yielded better clinical outcomes than the 3-month GnRH-a therapy but at a higher cost. Despite the lower monthly cost of oral contraceptive therapy, the ICERs for oral contraceptive therapy over no medical therapy were all greater than the per capita GDP of China for all four types of endometriosis, which indicates that oral contraceptive therapy is not a cost-effective option in the Chinese setting. This finding also indicate that the strategy of short-term of GnRH-a combining long-term of OC therapy should be considered as an alternative in the future clinical studies.

GnRH agonists have been shown to relieve the painful symptoms associated with endometriosis and to increase the duration of improvement when used for 6 months after surgery[11]. A one-way sensitivity analysis showed that the parameters related to the remission rate were the most influential. This finding suggested the ability of GnRH agonists to increase the remission rate and decrease the endometriosis recurrence rate following conservative surgery to be major determinants of clinical and economic outcomes. It could be hypothesized that maintaining the efficacy of medical or conservative surgical interventions may improve their cost-effectiveness. However, more than 50% of patients will experience the recurrence of pain within 5 years when medical therapy is discontinued, and the risk of recurrence will remain unchanged, as this risk is only delayed for the duration of the therapy[13]. Currently, new regimens, such as aromatase inhibitors plus GnRH-a, are under investigation in clinical trials[36]. Other independent and influential parameters include the utility scores associated with endometriosis, which have suggested that capturing accurate quality of life data is essential[12]. The model outcome was not sensitive to the parameter associated with ovarian cancer, although an association of a history of endometriosis with an increased risk of ovarian cancer was apparent[25]. The potential reason for this result is that the incidence of ovarian cancer is too low for the model to capture a notable impact. An appropriate surveillance plan for ovarian cancer in a population with endometriosis should be further investigated.

Strengths and limitations

There was great excitement among uterologists and patients after clinical studies demonstrated the health benefits of GnRH agonists for endometriosis. However, in the context of limited health resources, the widespread use of GnRH-a increases the financial burden on patients and societies. To our knowledge, this is the first study to perform an economic evaluation of the use of oral contraceptive therapy and GnRH agonist therapy to prevent recurrent endometriosis following conservative surgery. Ovarian cancer was included in the model as one of the outcomes. The finding indicates that postoperative medical therapy might be helpful for reducing a paucity (~0.1%) of the risk of ovarian cancer associated with endometriosis. Although the current analysis focused on the Chinese setting, the economic findings also might be a reference for decision makers from other medium-income regions, such as Brazil, Russia, Taiwan and Thailand. The evidence of improved health benefits providing by GnRH-a also might be helpful for worldwide clinicians and patients who want to make a decision if GnRH-a should be used as a first-line treatment.

Our study had several limitations that require consideration. First, the current study used the clinical data driving from different published sources to evaluate the health and economic outcomes of the four strategies due to the absence of direct head-to-head studies comparing the OC, 3- and 6-month GnRH-a

strategies with no medical therapy. This generates uncertainty regarding the findings because the data from the different sources had a high degree of heterogeneity due to the varied study designs, patient characteristics, and dosing schedules. To test the robustness of the results, sensitivity analyses were carried out by adjusting the model variables. Future analyses should be updated if head-to-head data become available. Second, the risk of recurrence of endometriosis may be considerably different in the future, especially as new therapies are introduced[36]. To simplify our evaluation, we did not account for this issue. Nevertheless, our finding that the 6-month GnRH-a strategy is a very cost-effective alternative to the conservative treatment strategy indicates that it should be recommended and covered by health insurance. Third, we did not project the "continuous treatment effect" approach under which active treatments, especially GnRH-a treatments, are prescribed beyond 6 months because the efficacy and safety of continuous GnRH-a treatment beyond this period requires evidence from more well-designed clinical studies [9]. Fourth, this study excluded indirect costs, such as the loss of productivity. One multicenter cross-sectional study showed that endometriosis can impair quality of life and work productivity. The loss of work productivity translated into significant costs per woman/week, from US$4 in Nigeria to US$456 in Italy[37]. If these indirect costs were included, the cost-effectiveness of active treatment may be improved because indirect costs would be saved. Fifth, the present analysis did not account for changes in health-resource expenditures or quality of life due to treatment-related adverse events. The economic outcome of active medical prevention over no prevention would become less favorable if such burdens were considered; however, the available evidence suggests that active medical prevention is usually so well tolerated that women's quality of life often improves with therapy, with minimal impact on the cost or quality of life[38-40]. Finally, due to the absence of the trials comparing the efficacy other potential competitions between GnRH-a and evonorgestrel-releasing intrauterine system or depot medroxy progesterone acetate the recurrence after surgery, the current analysis did not evaluate these potential competitions for avoiding the considerable uncertainty.

Interpretation

The current ESHRE guidelines recommend postoperative treatment with long-term GnRH-a to reduce endometriosis-associated pain and to delay recurrence [7]. Our findings indicate that this recommendation may be reasonable because the economic outcomes associated with long-term GnRH-a use are more favorable than those associated with short-term use. Our findings were partly in accordance with those from the report recently published by Sanghera S *et al*[12]. From a UK National Health Service perspective, the authors evaluated the cost-effectiveness of a levonorgestrel-releasing intrauterine system, depot-medroxyprogesterone acetate, and the combined oral contraceptive pill for preventing the recurrence of endometriosis after conservative surgery in primary care over a 3-year period. They found that none of the strategies was significantly beneficial compared with no treatment due to their expensive costs and fewer QALYs. Our results also indicated that oral contraceptive therapy was not a dominant strategy due to its limited clinical efficacy. However, GnRH agonist therapy was not taken into account in their analysis. Our findings may provide reference information for patients, physicians, and decision-makers when therapy based on GnRH agonists is considered.

Conclusion

In conclusion, 6-month GnRH-a therapy is highly cost-effective compared with no medical therapy in women with endometriosis after conservative surgery because of the favorable ICER in the Chinese health care setting. Due to the uncertainty regarding the findings, future analyses are necessary when more reliable data become available.

Contributors

YW and BW conceptualized the study, designed the analysis, and wrote the final manuscript. YY and RGT performed the literature search. YW and BW prepared and conducted the analysis. YW is the guarantor of the study.

Declaration of interests

All authors declare no competing interests. The ICMJE disclosure forms are available as online supporting information.

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Details of ethics approval

This is an economic analysis and does not require ethical approval.

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References:

[1] Vercellini P, Vigano P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014; 10: 261-75.

[2] Hickey M, Ballard K, Farquhar C. Endometriosis. BMJ. 2014; 348: g1752.

[3] Ozkan S, Murk W, Arici A. Endometriosis and infertility: epidemiology and evidence-based treatments. Ann N Y Acad Sci. 2008; 1127: 92-100.

[4] Parazzini F, Esposito G, Tozzi L, Noli S, Bianchi S. Epidemiology of endometriosis and its comorbidities. Eur J Obstet Gynecol Reprod Biol. 2016.

[5] Lee WL, Chang WH, Wang KC, Guo CY, Chou YJ, Huang N, et al. The Risk of Epithelial Ovarian Cancer of Women With Endometriosis May be Varied Greatly if Diagnostic Criteria Are Different: A Nationwide Population-Based Cohort Study. Medicine (Baltimore). 2015; 94: e1633.

[6] Soliman AM, Yang H, Du EX, Kelley C, Winkel C. The direct and indirect costs associated with endometriosis: a systematic literature review. Hum Reprod. 2016; 31: 712-22.

[7] Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014; 29: 400-12.

[8] Guo SW. Recurrence of endometriosis and its control. Hum Reprod Update. 2009; 15: 441-61.
[9] Tafi E, Leone RMU, Alessandri F, Bogliolo S, Gardella B, Vellone VG, et al. Advances in pharmacotherapy for treating endometriosis. Expert Opin Pharmacother. 2015; 16: 2465-83.
[10] Zheng Q, Mao H, Xu Y, Zhao J, Wei X, Liu P. Can postoperative GnRH agonist treatment prevent endometriosis recurrence? A meta-analysis. Arch Gynecol Obstet. 2016; 294: 201-7.
[11] Olive DL. Gonadotropin-releasing hormone agonists for endometriosis. N Engl J Med. 2008; 359: 1136-42.
[12] Sanghera S, Barton P, Bhattacharya S, Horne AW, Roberts TE. Pharmaceutical treatments to prevent recurrence of endometriosis following surgery: a model-based economic evaluation. Bmj Open. 2016; 6: e10580.
[13] Somigliana E, Vercellini P, Vigano P, Benaglia L, Busnelli A, Fedele L. Postoperative medical therapy after surgical treatment of endometriosis: from adjuvant therapy to tertiary prevention. J Minim Invasive Gynecol. 2014; 21: 328-34.
[14] Singh SS, Suen MW. Surgery for endometriosis: beyond medical therapies. Fertil Steril. 2017.
[15] Xuan Z, Jun-li L, Shi-rong C, Yi L. Analysis of relative factors influencing recurrence of endometriosis after operation treatment. Chinese Journal of Obstetrics and Gynecology. 2006; 41: 669-71.
[16] Crosignani P, Olive D, Bergqvist A, Luciano A. Advances in the management of endometriosis: an update for clinicians. Hum Reprod Update. 2006; 12: 179-89.
[17] Li L, Wu J, Jiang XQ, Pu DH, Zhao Y. Survey on epidemiologic factors associated with the age of natural menopause and menopausal symptoms in Jiangsu women. Zhonghua Fu Chan Ke Za Zhi. 2013; 48: 728-33.
[18] Task Group of the Chinese Guidelines for Pharmacoeconomic Evaluations： China Guidelines for Pharmacoeconomic Evaluations. China Journal of Pharmaceutical Economics. 2011; 6: 7-48.
[19] Murray CJ, Evans DB, Acharya A, Baltussen RM. Development of WHO guidelines on generalized cost-effectiveness analysis. Health Econ. 2000; 9: 235-51.
[20] Busacca M, Chiaffarino F, Candiani M, Vignali M, Bertulessi C, Oggioni G, et al. Determinants of long-term clinically detected recurrence rates of deep, ovarian, and pelvic endometriosis. Am J Obstet Gynecol. 2006; 195: 426-32.
[21] Wu L, Wu Q, Liu L. Oral contraceptive pills for endometriosis after conservative surgery: a systematic review and meta-analysis. Gynecol Endocrinol. 2013; 29: 883-90.
[22] Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998; 280: 1690-1.
[23] Dong-Li K. Advances in the long-term medical therapy for the prevention of recurrent endometriosis after conservative surgery. Journal of Practical Obstetrics and Gynecology. 2015; 31: 19-22.
[24] Cheong Y, Tay P, Luk F, Gan HC, Li TC, Cooke I. Laparoscopic surgery for endometriosis: How often do we need to re-operate? J Obstet Gynaecol. 2008; 28: 82-5.
[25] Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol. 2012; 13: 385-94.
[26] Wang B, Liu SZ, Zheng RS, Zhang F, Chen WQ, Sun XB. Time trends of ovarian cancer incidence in China. Asian Pac J Cancer Prev. 2014; 15: 191-3.
[27] Wong KH, Mang OW, Au KH, Law SC. Incidence, mortality, and survival trends of ovarian cancer in Hong Kong, 1997 to 2006: a population-based study. Hong Kong Med J. 2012; 18: 466-74.
[28] Melin AS, Lundholm C, Malki N, Swahn ML, Sparen P, Bergqvist A. Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer. Acta Obstet Gynecol Scand. 2013; 92: 546-54.
[29] Yao-di L, Yun L. Analysis of Cost-effectiveness and Adverse Reactions of Three Drugs in the Treatment of

Endometriosis after Conservative Surgery. Strait Pharmaceutical Journal. 2015; 27: 230-2.
[30] Liu X, Zhang HX, Wang LP, Fu WP. Application of half-dose depot long-acting triptorelin in postoperative adjuvant therapy for endometriosis. Zhonghua Yi Xue Za Zhi. 2013; 93: 208-11.
[31] Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol. 2004; 191: 733-40.
[32] Li L, Leng JH, Lang JH. Economics analysis of endometriosis and adenomyosis surgeries. Zhonghua Yi Xue Za Zhi. 2011; 91: 2619-22.
[33] Yi Z, Ya-Na B, Xiao-Bi H, Chi Z, Hong-bao M, Xian S. Trends of Disease Economic Burden of Three Common Cancers in Women Patients in Rural Areas. Chinese General Practice. 2012; 15: 3300-2.
[34] Manchanda R, Legood R, Burnell M, McGuire A, Raikou M, Loggenberg K, et al. Cost-effectiveness of population screening for BRCA mutations in Ashkenazi jewish women compared with family history-based testing. J Natl Cancer Inst. 2015; 107: 380.
[35] Xiao-fang S. The pharmacoeconomic analysis of three schemes in treatment of endometriosis using laparoscopy. Strait Pharmaceutical Journal. 2010; 22: 202-4.
[36] Lindsay SF, Luciano DE, Luciano AA. Emerging therapy for endometriosis. Expert Opin Emerg Drugs. 2015; 20: 449-61.
[37] Nnoaham KE, Hummelshoj L, Webster P, D'Hooghe T, de Cicco NF, de Cicco NC, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril. 2011; 96: 366-73.
[38] DiVasta AD, Feldman HA, Sadler GJ, Stokes NA, Laufer MR, Hornstein MD, et al. Hormonal Add-Back Therapy for Females Treated With Gonadotropin-Releasing Hormone Agonist for Endometriosis: A Randomized Controlled Trial. Obstet Gynecol. 2015; 126: 617-27.
[39] Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. Obstet Gynecol. 2002; 99: 709-19.
[40] Berlanda N, Somigliana E, Vigano P, Vercellini P. Safety of medical treatments for endometriosis. Expert Opin Drug Saf. 2016; 15: 21-30.

Figure captions:

Figure 1. The structure of the decision model with a decision tree (A) and the Markov model of long-term complications (B). GnRH-a: gonadotropin-releasing hormone agonist.

Figure 2. Cost-effectiveness acceptability curves showing the probability of 4 competing strategies for a range of cost-effectiveness thresholds stratified by four types of endometriosis.

Table 1. Key clinical data*.

Parameter	Values(ranges)	Distributions	Description and Reference
Probability of recurrence for ovarian endometriosis with no prevention ≤4 years#	0.0028 (0.0021 - 0.0035)	Beta(α=61.29, β=22002.78)	[21]
Probability of recurrence for peritoneal endometriosis with no prevention ≤4 years#	0.0054 (0.0041 - 0.0068)	Beta(α=61.13, β=11196.41)	[21]
Probability of recurrence for deep endometriosis with no prevention ≤4 years#	0.0067 (0.0051 - 0.0084)	Beta(α=61.05, β=9004.55)	[21]
Probability of recurrence for other endometriosis with no prevention ≤4 years#	0.0033 (0.0025 - 0.0041)	Beta(α=61.26, β=18464.17)	[21]
Probability of recurrence for ovarian endometriosis with no prevention 5-8 years#	0.0039 (0.0029 - 0.0049)	Beta(α=61.23, β=15625.61)	[21]
Probability of recurrence of ovarian endometriosis with no prevention 5-8 years#	0.0011 (0.0008 - 0.0013)	Beta(α=61.4, β=57739.29)	[21]
Probability of recurrence of peritoneal endometriosis with no prevention 5-8 years#	0.0021 (0.0016 - 0.0026)	Beta(α=61.34, β=29460.01)	[21]
Probability of recurrence of deep endometriosis with no prevention after 5-8 years#	0.0032 (0.0024 - 0.0041)	Beta(α=61.27, β=18822.04)	[21]
RR of recurrence of OCT versus surgery	0.33 (0.24 - 0.47)	Normal(μ=0.33, σ=0.06)	[10, 11]
RR of recurrence of GnRH-3 versus OCT	0.88 (0.43 - 1.9)	Normal(μ=0.88, σ=0.38)	[10, 11]
RR of recurrence of GnRH-6 versus OCT	0.54 (0.28 - 1.12)	Normal(μ=0.54, σ=0.21)	[10, 11]
Proportion of receiving surgery again after recurrence	0.51 (0.25 - 0.53)	Beta(α=24.98, β=24)	[24]
Clinical remission rate of OCT	0.67 (0.6 - 0.79)	Beta(α=61.05, β=30.53)	[10]
Clinical remission rate of surgery	0.39 (0.21 - 0.57)	Beta(α=10.9, β=17)	[10]
OR of clinical remission rate OCT versus GnRH-a	0.25 (0.06 - 1)	Normal(μ=0.25, β=0.24)	[10]
Incidence of ovarian cancer in general Chinese women	0.000054 (0.000048 - 0.000061)	Beta(α=260.24, β=4863990.75)	[26]
RR of ovarian cancer in women with endometriosis	1.56 (1.4 - 1.74)	Normal(μ=1.56, β=0.09)	[25]
RR of ovarian cancer of receiving surgery (no recurrence) versus no surgery (recurrence)	0.37 (0.16 - 0.79)	Normal(μ=0.37, β=0.16)	[28]
Probability of death causing by ovarian cancer	0.0071 (0.0062 - 0.008)	Beta(α=242.42, β=34008.8)	[27]

* Probabilities were showed as per Markov cycle

It was calculated by the following formula: $\text{Probability}_{\text{cycle}} = 1-(1-\text{Cumulative probability}_{\text{n year}})^{(1/\text{n year})}$

Abbreviations: GnRH: gonadotropin-releasing hormone; OCT: oral contraceptive therapy; RR: risk ratio.

Table 2. Summary of Cost ($) and Outcome Results in base-case analysis.

Strategy	Cost	QALYs	LYs	Cumulative probability of ovarian cancer(%)	Incremental cost per QALY*
Ovarian endometriosis					
No medical therapy (Control strategy)	2,779	6.61	17.78	0.813%	NA
OC strategy	8,036	7.10	17.78	0.713%	10,684
GnRH-3 strategy	8,841	7.40	17.78	0.713%	7,709
GnRH-6 strategy	9,650	7.69	17.78	0.710%	6,364
Peritoneal endometriosis					
No medical therapy (Control strategy)	2,474	6.58	17.78	0.794%	NA
OC strategy	7,941	7.09	17.78	0.703%	10,630
GnRH-3 strategy	8,743	7.38	17.78	0.702%	7,759
GnRH-6 strategy	9,543	7.68	17.78	0.697%	6,425
Deep endometriosis					
No medical therapy (Control strategy)	3,161	6.64	17.77	0.841%	NA
OC strategy	8,015	7.10	17.78	0.723%	10,589
GnRH-3 strategy	8,817	7.39	17.78	0.722%	7,523
GnRH-6 strategy	9,614	7.68	17.78	0.717%	6,185
Other endometriosis					
No medical therapy (Control strategy)	2,655	6.60	17.78	0.808%	NA
OC strategy	7,996	7.10	17.78	0.710%	10,728
GnRH-3 strategy	8,800	7.39	17.78	0.710%	7,759
GnRH-6 strategy	9,608	7.69	17.78	0.707%	6,407

* Comparing with Control strategy

Abbreviations: GnRH: gonadotropin-releasing hormone; OC: oral contraceptive; QALY: quality-adjusted life-years; LY: life-years; NA: not applicable.